

CARDIOVASCULAR, PHARMACOLOGY and CHEMISTRY

THE COUNCIL FOR TOBACCO RESEARCH - U.S.A.

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633 THIRD AVENUE
NEW YORK, N. Y. 10017
Renewal

Application for Research Grant

No. 492R1

Activated: 7/1/65

Date: February 1, 1966

1. Name of Investigator: Dr. Walter M. Booker, Dr. S. N. Pradhan, and
Dr. T. A. Balourdas
2. Title: Professor & Head, Department of Pharmacology, Professor and
Assistant Professor, respectively.
3. Institution & Address: Howard University
520 W Street, N. W.
Washington, D. C.
4. Project or Subject: "Studies on the Possible Sensitization of the
Vascular Mechanism to Catecholamines Following Nicotine Administration"

5. Detailed Plan of Procedure (Use additional pages if more space is required.)

Current Experiments and Experiments Planned for the Next Year:

At present the experiments reported in the abstracts (attached) are being conducted along the lines mentioned. We plan to expand these experiments as various developments occur. In addition to these experiments, we plan to start the following experiments:

1. Cardiac catecholamine depletion by daily injections (every three hours or more often) of nicotine in normal and scorbutic guinea pigs.
2. Influence of nicotine on resynthesis of cardiac catecholamines in normal and scorbutic guinea pigs.
3. Sensitivity of the isolated hearts of guinea pigs to norepinephrine and to angiotensin following nicotine administration (perfused for 10 to 15 minutes).
4. The responses of hypertensive dogs to nicotine doses; comparison with normotensive responses.

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In vivo experiments have shown the development of vascular hyperreactivity induced by nicotine. The observations were made on the microvascular system of rats by direct visualization of the minute mesoappendiceal vasculature under the microscope after administration of nicotine (35-40 $\mu\text{g/kg}$). (See copy of abstract attached.)

Further experiments are designed to determine whether or not nicotine administered to animals subjected previously to abnormal pathophysiological conditions causes the same effects on the microvessels, as above mentioned, or its effects are more prominent, different and/or exaggerated. Specifically, the rats should be subjected to experimental diabetes mellitus by alloxanization or by pancreatectomy with the possible development of microangiopathy, as is expected in diabetic conditions.

Using the same bioassay technique of the rat mesocaecum preparation, we shall be able to obtain direct observations of the effect of nicotine on two groups of experimental animals, viz.

- (a) Rats treated with nicotine previously being normal, and used as control groups; and
- (b) Rats diabetic become experimentally used to test the effect of nicotine administration on already hypersensitive capillary vessels

The development of vascular hyperreactivity and other morphological and functional changes in abnormal conditions may have several clinical implications and many morbid entities should be explainable by their existence. Secondary adjunctive potentialities might be precipitated and aggravated by predisposed hyperreactive blood vessels and vice versa. Such hypersensitive vessels appear more hyperreactive to normally and abnormally discharged and circulating endogenous amines as well as to exogenous vasoactive agents and factors.

Further studies on the responses of the blood pressure and the somatic reflexes to various doses of nicotine injected into lateral ventricle are intended in future experiments. These studies are to be extended after administration of the compound into the third and the fourth ventricles and also in the various parts of the lateral ventricle as have been demonstrated in the case of d-tubocurarine by Feldberg and his associates. Microelectrophoresis of nicotine into several subcortical sites may also be attempted.

On blood pressure, the pattern of response needs further confirmation and analysis of the response into possible components is intended by usual physiological and pharmacological means.

Studies on the effect of nicotine on reflexes will be extended to other somatic and autonomic reflexes involving supraspinal sites. Its effects on some central structures, such as reticular formation, hippocampus, hypothalamus and others will be investigated by studying the changes in the responses of blood pressure, various reflexes or other physiological functions induced by stimulation of these structures after central administration of nicotine.

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This work will be organized in the same way as currently organized; that is, sections of it will be pursued under the direction of the staff persons named in this grant. Graduate students, research assistant (now employed) will be used in the work.

Papers Published or Presented at National Meetings:

"Blood Pressure Responses to Epinephrine and to Norepinephrine Following Nicotine Administration"

Presented at the Fall Meeting of the American Society for Pharmacology and Experimental Therapeutics. This paper is now being prepared for publication.

Experiments pursued during the past six months:

The attached abstracts of papers which will be presented at the Federation meetings in Atlantic City, April 9-15, 1966 can best describe the work that has been in progress.

BUDGET

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Personnel

Research Assistant GS-6
Staff Benefits

\$ 5702.00
342.00

Expendable Supplies

Animals, Glassware, etc.

3000.00

Other Expenses

Student Stipends & Tuition

4347.00

Travel

500.00

Other contractual services

200.00

Permanent Equipment

1000.00

Overhead

2114.00

Total

\$17205.00

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6. Budget Plan:

a. Salaries	\$ 5702.00
b. Expendable Supplies	3000.00
c. Other Expenses	5389.00*
d. Permanent Equipment	1000.00
e. Overhead (15% of a, b, c)	2114.00
Total	\$17205.00

*See itemization of "other expenses".

7. Anticipated Duration of Work: Two years.

8. Facilities and Staff Available: Well-equipped laboratories, animal quarters, apparatus for cardiovascular and neuropharmacological and other types of measurements. Spectrofluorometer for estimating catecholamines. Facilities for studying numerous isolated organ preparations.

Staff is active in research. Graduate students take part in research with and under direction of the staff.

9. Additional Requirements:

10. Additional Information (including relation of work to other projects and other sources of support):

Same as indicated on original application.

Signature

Director of Project

Business Officer of the Institution

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